REMARKS

I. Status of the Claims

Claims 246-252, 255, 264, 265 and 271-275 were pending and examined in the March 10, 2010 Office Action. With this Reply, claims 246, 255, 264, 271 and 273 are amended, claims 272 and 275 are newly canceled and claims 276-279 are newly added to more particularly point out and distinctly claim the invention. The claim amendments are made without prejudice or disclaimer and introduce no new matter. The claim amendments are supported at least at FIG. 2 and pages 34-47 of the specification as filed. Claims 246-252, 255, 264, 265, 271, 273, 274, 276 and 277 are presented for reconsideration.

II. Double Patenting

Claims 246-252, 255, 264, 265 and 271-275 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting (OPD) as being unpatentable over claims 245-248, 251, 253, 261-265, 306 and 307 of copending Application No. 08/978,633. Since this rejection is dependent on the scope of both the instant claims and the claims in the cited application, Applicants will provide terminal disclaimers where necessary when proper ODP rejections are the only rejections remaining in this application.

III. Rejections under 35 U.S.C. § 102(b)

(a) Claims 246-252, 255, 264, 265 and 271-275 are rejected under 35 U.S.C. 102(e) as being anticipated by Craig et al. (U.S. Patent No. 5,766,902). The Action asserts that Craig et al. "taught methods for enhancing the targeted delivery of nucleic acid molecules to cells by coupling the nucleic acid to a ligand having affinity for a cell surface molecule or receptor." The Action also cites col. 4 and 8 of Craig et al. as teaching fusogenic peptides as the ligand and interprets the examined claims as encompassing only one ligand by reading the fusogenic peptide and the ligand of claim 246 as encompassing embodiments where they are the same entity.

Applicants respectfully request reconsideration and withdrawal of this rejection in light of the claim amendments and the following discussion.

Applicants first note that the skilled artisan would clearly not consider the fusogenic peptide as recited in claim 246 to also be the ligand to a cell receptor specified therein. As indicated in Craig et al., at Col. 8, lines 28-45, a fusogenic peptide, *e.g.*, as exemplified with the influenza hemaggutinin fusogenic peptide, allows for fusion of the targeted DNA/ligand complex to a cell membrane "but without the host cell sialic acid-binding specificity" which is conferred by a separate ligand/receptor interaction. See also Wagner et al., Proc. Natl. Acad. Sci. USA 89:6099-6103 (1992), provided with the Information Disclosure Statement filed on October 27, 2003, where a noncovalent mixture of DNA, transferrin and the influenza fusogenic peptide covalently linked to polylysine are used. In that work, the transferrin was used as a ligand for cell entry via endocytosis, and after internalization the fusogenic peptide allowed release from the endosomes. Thus, the skilled artisan would understand that the "fusogenic peptide" recited in claim 246 as amended could not be considered a ligand. Applicants note that, to provide further clarity on this issue, claim 246 has been amended to recite "a fusogenic peptide" and "a ligand to a cell receptor." Applicants also note that claim 246 as amended further recites the presence of a third nucleotide modification, comprising an entity that confers nuclear localization. Such a construct having three nucleotide modifications is illustrated at least in FIG. 2. Applicants assert that Craig et al. does not teach or suggest the construct recited in claim 246 as amended.

At page 11, the Office Action asserts that Craig et al. discloses the feature of claim 271 that "solely one strand of said construct comprises a modified nucleotide..." by stating that "in such constructs, the polypeptide would necessarily be conjugated to one strand." This ignores the limitation "on **only** one strand" (emphasis added). Such a feature is not taught or suggested by Craig et al. Furthermore, the specification presents a discussion of the advantages of the use of only particular parts (*e.g.*, one strand) of a nucleic acid construct having modifications. For instance on page 34, the specification states "one or more of the above properties is capable of being provided without substantially interfering with the biological function of said nucleic

acid." Additionally, on page 39 the specification states "[s]uch single stranded regions can serve as a means to segregate biological function from other functions and as regions for complementarity for the binding of nucleic acids (as in Example 6b)." Also, pages 46-47 state:

> The present invention provides for choice of localization of ligands or chemical modifications. In order that such ligands or chemical modifications do not interfere with biological activity[,] segments with biological activity can be isolated form modified segments in the CHENAC. Also, modifications can be confined to a region or a segment. For example, a specific primer labeled with Ligands or chemical modifications of choice can be hybridized to a defined region of the construct, and polymerization can be done in the presence [of] unmodified nucleotides in order to confine the ligands or chemical modifications to a defined area of the primer. Alternatively, by using a primer containing ligands or chemical modifications, labeling can be done throughout the strand or through complementarity to a tail.

Thus, the specification indicates that a strand that is used as template for transcription may advantageously remain unmodified through the proper design of constructs that contain modified nucleotides. Various means for making such constructs are described, for example, in Examples 1-5 and illustrated in FIGS. 1-4. It can be clearly seen in these various examples and figures that one strand remains unmodified. Craig et al., provides no indication that multiple modifications on a construct could advantageously be made on only one strand. Therefore, Craig et al. does not anticipate this aspect of the claims.

In light of the claim amendments and the above discussion, withdrawal of the rejection of claims 246-252, 255, 264, 265 and 271-275 under 35 U.S.C. 102(e) as being anticipated by Craig et al. is respectfully requested.

(b) Claims 246-249, 252, 255, 264, 265 and 274 are rejected under 35 U.S.C. 102(b) as being anticipated by Hirsch et al. (1993) Transplantation Proceedings 25:138-139. The Action asserts that "Hirsch et al. taught a method for the targeted transfection of plasmid DNA, comprising covalently coupling the DNA to a monoclonal antibody." The Action further asserts that the monoclonal antibody is a fusogenic protein, and thereby a ligand. Applicants request

reconsideration and withdrawal of this rejection in light of the claim amendments and the following discussion.

As discussed in **(a)** above, the instant claims are directed to nucleic acid constructs comprising multiple modifications. By contrast, the DNA described by Hirsch et al. only has one modification – a monoclonal antibody conjugated thereto. As such, Hirsch et al. does not anticipate the claims. Accordingly, withdrawal of the rejection of claims 246-249, 252, 255, 264, 265 and 274 under 35 U.S.C. 102(b) as being anticipated by Hirsch et al. is respectfully requested.

IV. Rejections under 35 U.S.C. § 103(a)

Claims 250, 251, 271, 272, 273 and 275 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hirsch et al. (discussed under **III.(b)** above), in view of Keating et al. (U.S. Patent 6,503,755), Bos et al. (Hybridoma 11:41-51, 1992), and Smith-Ravin et al. (Int. J. Radiat. Biol. 56:951-961, 1989). The Action asserts that Hirsch et al. teaches all of the limitations of the claims except for linearized plasmids or excluding the antibody to one strand; and that Keating et al. and Bos et al. teach improving methods for transfecting mammalian cells with plasmid DNA by linearizing the plasmids. With respect to claims 273-275, the Action further asserts that Smith-Ravin et al. teach the use of ionizing radiation to prepare nicked plasmid DNA for transfection into Chinese hamster ovary cells. The Action deems this combination of references to make the subject claims obvious. Applicants respectfully request reconsideration and withdrawal of this rejection in light of the claim amendments and the following discussion.

As discussed in **III.(b)** above, the instant claims are directed to nucleic acid constructs comprising multiple modifications, but Hirsch et al. only teaches or suggests DNA comprising one modification. Additionally, neither Keating et al., Bos et al., nor Smith-Ravin et al. teach a nucleic acid construct comprising more than one modification.

With respect to claim 271, the Action asserts that "[o]ne of skill would further reasonable have concluded that constructs in which the antibody is coupled to one strand or both strands

would have substantially the same properties and would produce substantially the same effects." Applicants disagree, and point to the discussion under **III.(a)** above, where it is explained that limiting the modifications to "solely one strand" as recited in claim 271 has distinct advantages that are not taught or suggested by Hirsch et al., Keating et al., Bos et al., or Smith-Ravin et al. For example, limiting the modifications to one strand avoids any interference from the modifications to transcription, which can proceed from the unmodified strand.

Since none of the cited references, alone or in combination, teach or suggest (a) a nucleic acid construct comprising more than one modification, or (b) a construct having modifications only on one strand, as claimed, the cited combination of references do not make the instantly claimed compositions obvious. Withdrawal of the rejection of claims 250, 251, 271, 272, 273 and 275 under 35 U.S.C. 103(a) is thus respectfully requested.

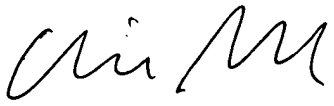
V. Conclusion

In view of the foregoing remarks, Applicants respectfully request withdrawal of all rejections and passage of claims 246-252, 255, 264, 265, 271, 273, 274, and 276-279 to allowance.

No other fee or fees are believed due in connection with this paper. In the event that any fee or fees are due, however, the United States Patent and Trademark Office is hereby authorized to charge any such fee or fees to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney requests that he be contacted at the number provided below.

Respectfully submitted,



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